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Mini Review **Open Access**

Use of dexamethasone in the management of respiratory tract infections

*[1]Adegboro, B., [2]Abayomi, S. A., [1]Imran, J., and [3]Sanni, E. O.

[1]Department of Medical Microbiology and Immunology, Nile University of Nigeria, Abuja, Nigeria
[2]Department of Medical Microbiology, LAUTECH Teaching Hospital, Ogbomoso, Nigeria
[3]Department of Haematology, Nile University of Nigeria, Abuja, Nigeria
*Correspondence to: boazadegboro@gmail.com

Abstract:

Dexamethasone is a potent synthetic member of the glucocorticoid class of corticosteroid drugs that has been useful for the management of some pathological disorders because it affects a protean number of signaling pathways. It is used as adjunct therapy in the management of sepsis, arthritis, cardiac transplant, blood, hormone/immune system disorders, allergic reaction, skin, eye conditions, cancer and other pathologic disorders and as a mainstay of therapy in autoimmune hepatitis. With the advent of COVID-19, there have been investigations of its use as anti-inflammatory agent in severely ill patients. This present review elucidates the various studies on the use of dexamethasone in the management of severe respiratory tract infections, with the ultimate aim of reducing mortality amongst severely ill patients, including COVID-19.

Keywords: dexamethasone; adjunctive therapy; respiratory infections; COVID-19

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Utilisation de la dexaméthasone dans la prise en charge des infections des voies respiratoires

*[1]Adegboro, B., [2]Abayomi, S. A., [1]Imran, J., et [3]Sanni, E. O.

[1]Département de microbiologie médicale et d'immunologie, Université du Nil du Nigéria, Abuja, Nigéria
[2]Département de microbiologie médicale, Hôpital universitaire LAUTECH, Ogbomoso, Nigéria
[3]Département d'hématologie, Université du Nil du Nigéria, Abuja, Nigéria
*Correspondance à: boazadegboro@gmail.com

Abstrait:

La dexaméthasone est un membre synthétique puissant de la classe des corticostéroïdes glucocorticoïdes qui a été utile pour la gestion de certains troubles pathologiques car elle affecte un nombre protéiforme de voies de signalisation. Il est utilisé comme traitement d'appoint dans la prise en charge de la septicémie, de l'arthrite, de la transplantation cardiaque, du sang, des troubles hormonaux/du système immunitaire, des réactions allergiques, des affections cutanées, oculaires, du cancer et d'autres troubles pathologiques et comme pilier du traitement de l'hépatite auto-immune. Avec l'avènement du COVID-19, des études ont été menées sur son utilisation comme agent anti-inflammatoire chez des patients gravement malades. Cette revue présente les différentes études sur l'utilisation de la dexaméthasone dans la prise en charge des infections sévères des voies respiratoires, dans le but ultime de réduire la mortalité chez les patients gravement malades, y compris le COVID-19.

Mots clés: dexaméthasone; thérapie d'appoint; infections respiratoires; COVID-19

Introduction:

Dexamethasone is a potent synthetic member of the glucocorticoid class of corticosteroid drugs (1). It was found useful for managing some pathological disorders because it affects a protean number of signaling pathways. These effects may explain its therapeutic benefits when used in the management of sepsis, arthritis, cardiac transplant, blood, hormone/immune system disorders, allergic reaction, skin, eye conditions, cancer and other pathologic disorders (1). Dexamethasone is synthesized by dehydration of 16 β-methylprednisolone acetate to give the 9,11 dehydro derivative, which is then reacted with a hydrobromite source such as basic N, bromosuccinimide to form 9α-bromo 11-β hydrin derivative, and the ring is then closed to form an epoxide. A ring opening reaction with hydrogen fluoride in tetrahydrofuran gives rise to dexamethasone (2). The adrenal glands also produce corticosteroids naturally (3). These are steroid hormones which play important physiologic roles in the body such as glucose and protein metabolisms, and suppression of immune and inflammatory processes (3).

Most children will be infected by respiratory syncytial virus (RSV) before the age of two years (3). About 1% of them will need to be admitted to the hospital while respiratory failure will occur in 5-8% of cases, necessitating mechanical ventilation (3). Aspergillosis, asthma, and allergic broncho-pulmonary pneumonia could cause reactive airway diseases, and corticosteroids could be useful in treatment of these conditions (4). Corticosteroids are also useful in the management of chronic obstructive pulmonary diseases (COPD), sarcoidosis, collagen vascular diseases, eosinophilic pneumonitis, idiopathic interstitial pneumonia and infectious disorders such as laryngo-tracheobronchitis (4). In addition, patients with influenza virus (H1N1 strain) and severe coronavirus infections often need mechanical ventilation, and dexamethasone could be useful in their management (4).

The efficacy of corticosteroids in the management of patients with RSV-LRTI (lower respiratory tract infection) has been studied over the years with conflicting results. While some studies found beneficial effects, many well-designed randomized control trials did not show that corticosteroids are beneficial. However, prednisolone shortened the length of hospital stay for patients on mechanical ventilation. A relevant research on influenza associated pneumonia showed that low-moderate dose of corticosteroid reduced mortality in patients with oxygen index lower than 300 mmHg (5). The purpose of this review is to assess the use of dexamethasone in the treatment of respiratory tract infections (RTIs) with emphasis on its use for patients with COVID-19.

Dexamethasone use in upper respiratory tract infections

The upper airway (nasopharynx, oropharynx, and laryngopharynx) conveys gases to and from the lungs, and filters, warms, and humidifies the air. The trachea and bronchi are lined by pseudo-stratified ciliated columnar epithelium which forms an active physical barrier against pathogens as an important part of the innate immunity (6). Goblet cells and mucus-producing glands are also included in this area and are responsible for producing roughly 100 ml of fluids/day in the adult, or more especially in disease state. All these provide protection against respiratory viral infections (6,7). However, despite these protective mechanisms, infection occurs by virus binding to specific receptors on epithelial cells of respiratory mucosa, thereby circumventing its removal by the mucociliary system or phagocytic cells (7).

Inspite of its clinical applications for up to 70 years, the role of corticosteroid as potent anti-inflammatory drug is still controversial in many pulmonary conditions (8). The role of dexamethasone in established viral infections such as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection (COVID-19), has been variously reported (7). Following entry into the cytoplasm of the cell by passive diffusion, glucocorticoids interact with glucocorticoid receptor (GR) to form a complex, which then moves into the nucleus where they either suppress or stimulate transcription, through a process called trans-repression or transactivation (9,10). Glucocorticoids inhibit transcription factors such as nuclear factor kappa B (NF-kβ) which are proteins that control the rate of transcription. Production of pro-inflammatory mediators by macrophages, eosinophils, lymphocytes, mast cells, and dendritic cells are controlled by these transcription factors. Also important is the inhibitory effect on phospholipase A2 that produce various inflammatory mediators (10,11).

Glucocorticoids also inhibits the genes responsible for expression of cyclooxygenase-2, inducible nitric oxide synthase, and proinflammatory cytokines, tumor necrosis factor alpha and interleukins (9). In contrast, corticosteroids initiate upregulation of lipocortin and of annexin A1, a protein that reduces prostaglandin and leukotriene synthesis and that also inhibits cyclooxygenase-2 activity and reduces

neutrophil migration to inflammatory sites. Because corticosteroid action occurs intracellularly, the effects persist, even when detection in the plasma is absent (9,10,12). Cytokine storm has been implicated as the mainstay in the pathogenesis of COVID-19 (13). The use of glucocorticoids will therefore have a place in the management of the disease. Dexamethasone is superior and preferred among other glucocorticoids due to its longer half-life and duration of action (24–36 hours), higher anti-inflammatory activities (30 times higher than cortisol and six times higher than triamcinolone), zero salt-retaining ability and most excellent penetration of lipid barriers for topical activity (10).

Dexamethasone use in lower respiratory tract infection

Following lower respiratory tract infection by any microorganism, cytokines and other inflammatory mediators are released by alveolar macrophages, which improves opsonization of the invading pathogens and usually lead to their successful removal (14). However, profound release of these cytokines and other inflammatory mediators can be detrimental to the host leading to significant damage to the lung parenchyma (14).

In a prospective study by Meduri et al., (15) involving 27 consecutive patients with acute respiratory distress syndrome (ARDS), patients who died from ARDS had raised levels of cytokines and inflammatory mediators on the first day of their admission and throughout their period of hospitalization. The persistent inflammatory response may contribute significantly to lung injury and subsequent respiratory failure. The need to abate the excessive release of cytokine and inflammatory mediators in lung infections using dexamethasone has generated wide interest among researchers, although the routine uses of systemic corticosteroid in the management of COVID-19 pneumonia has not been recommended by the World Health Organization (16). Administration of dexamethasone leads to reduction in serum levels of cytokines and inflammatory cells, which subsequently reduce the cytokine storm to the barest minimum. Mortality amongst very ill patients with ARDS is thus greatly reduced. Dexamethasone as a glucocorticoid as well as an anti-inflammatory steroid, suppress expression of pro-inflammatory genes (17).

Corticosteroids also help reduce tissue injury and edema, and this is believed to alleviate patient's distress from the accompanying inflammatory process after tissue injury. The effects of dexamethasone use on outcome in patients with pneumonia however remains controversial. In a prospective study by Monton et al., (18) on 27 patients with severe pneumonia on mechanical ventilation, glucocorticoid (GC), dexamethasone, alleviated patient's inflammatory response state. In this study, mortality rate in the patients who had treatment with GC was 36% (4/11), while for patients who did not receive GC, mortality rate was 67% (6/9). The survivors who received GC had reduced levels of serum TNF-α when compared to non survivors irrespective of their treatment with GC (18). It is good to note that despite the favorable outcome in reduction of risk of mortality reported in this study, other researchers have noticed a deleterious effect of use of corticosteroids in the treatment of lower respiratory tract infection. In the systematic review and meta-analysis involving 6548 patients, Ni et al., (19) reported that corticosteroid use could increase the death rate in patients with influenza pneumonia.

As dexamethasone suppresses immune reactions by inhibiting inflammatory responses, thus inhibiting the migration of inflammatory mediators from the circulation to issues via inhibition of the synthesis of chemokines and cytokines (19), the fear of researchers is that modulation of immune responses caused by these corticosteroids can elongate the period of viraemia and hinder viral clearance, thereby increasing the risk of mortality (20). The report of prospective study by Li et al., (5) involving 2141 hospitalized adolescent and adult patients with influenza A (H1N1) pdm09 viral pneumonia from 407 hospitals in mainland China, shows that low mortality rate was noticed in patients with severe disease treated with low-to-moderate dose corticosteroid, while patients with influenza pneumonia who had mild disease did not benefit from corticosteroid therapy. Meijvis et al., (22) also reported a significant reduction in the period of hospital admission in 304 adult patients diagnosed with community-acquired pneumonia and treated with intravenous dexamethasone (5 mg once a day) or placebo for 4 days at two teaching hospitals in the Netherlands. However, these patients also had antibiotics included in their treatment and were non-immunocompromised (21).

In a recent large randomized controlled study, 2104 patients with COVID-19 in the United Kingdom, randomly allocated to receive dexamethasone and other usual care (which included oxygen support, mechanical ventila tion/intensive care, treatment of intercurrent infections/diseases), were compared with 4321 patients concurrently allocated to usual care only without administration of dexamethasone.

Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation [29.0 vs 40.7%, age-adjusted rate ratio (RR); 0.65 (confidence interval 0.51 -0.82); p<0.001]; by one-fifth in patients receiving oxygen without invasive mechanical ventilation [1.5 vs 25.0%, RR 0.80 (95% CI 0.70 - 0.92); p=0.002); but did not reduce mortality in patients not receiving respiratory support at randomization (17.0 vs 13.2%, RR 1.22 (95% CI 0.93-1.61); p=0.14]. In patients hospitalized with COVID-19, dexamethasone reduced 28-day mortality among those receiving invasive mechanical ventilation or oxygen at randomization, but not among patients not receiving respiratory support (22).

Discussion:

Dexamethasone is derived from cortisol (hydrocortisone) (2). It plays important physiologic roles in the body such as glucose and protein metabolism, and suppression of immune and inflammatory processes (3). About 1% of children with RSV infection need to be admitted to hospital while respiratory failure progresses in 5-8% of them, necessitating mechanical ventilation (3). Patients with severe RSV, influenza virus (H1N1), and coronavirus infections often need mechanical ventilation, and dexamethasone could be useful in their management (4). Relevant research has also shown that influenza associated pneumonia in patients with oxygen index lower than 300 mmHg, low to moderate dose of corticosteroids significantly reduced mortality (5). Low oxygen index is a usual finding in COVID-19 patients with moderate to severe disease who require assisted ventilation. Although the role of corticosteroids as potent anti-inflammatory drugs is still controversial in the management of many pulmonary conditions, dexamethasone has been found useful in reducing mortality in established viral infections such as COVID-19 (7,8).

Among the glucocorticoids, dexamethasone is superior and preferred due to its longer half-life and duration of action (24–36 hours), its higher anti-inflammatory activities (30 times higher than cortisol and 6 times higher than triamcinolone), zero salt-retaining ability and most excellent penetration of lipid barriers for topical activity (10). In patients hospitalized with COVID-19, dexamethasone reduced 28-day mortality among those receiving invasive mechanical ventilation or oxygen at randomization, but not among patients not receiving respiratory support (22). It could therefore be safely concluded that patients with COVID-19 experiencing cytokine storm, particularly those on mechanical/assisted ventilation will benefit from treatment with dexamethasone.

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